METAPROTERENOL SULFATE - metaproterenol sulfate solution
Dey

PRESCRIBING INFORMATION
FOR INHALATION USE ONLY–NOT FOR INJECTION.

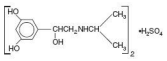
DESCRIPTION

Metaproterenol Sulfate Inhalation Solution USP is a unit-dose bronchodilator administered by oral inhalation with the aid of an intermittent positive pressure breathing apparatus (IPPB). It contains 0.4% or 0.6% metaproterenol sulfate in a sterile, acidic, aqueous solution containing edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide for pH adjustment.

Chemical, metraproterenol sulfate is 3,5 dihydroxy-α-[(isopropylamino)methyl] benzyl alcohol sulfate (2:1), a white crystalline, racemic mixture of two optically active isomers. It differs from isoproterenol hydrochloride by having two hydroxyl groups attached at the meta positions on the benzene ring rather than one at the meta and one at the para position.

$(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$
M.W. 520.59

Metaproterenol Sulfate



CLINICAL PHARMACOLOGY

Metaproterenol Sulfate is a potent beta-adrenergic stimulator with a rapid onset of action. It is postulated that beta-adrenergic stimulants produce many of their pharmacological effects by activation of adenyl cyclase, the enzyme which catalyzes the conversion of adrenosine triphosphate to cyclic adenosine monosphosphate.

Absorption, biotransformation and excretion studies following administration by inhalation have not been performed. Following oral administration in humans, an average of 40% of the drug is absorbed; it is not metabolized by catechol-O-methyltransferase but is excreted primarily as glucuronic acid conjugates.

Recent studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to human usage is currently unknown.

INDICATIONS AND USAGE

Metaproterenol Sulfate Inhalation Solution is indicated as a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Following controlled single dose studies by an intermittent positive pressure breathing apparatus (IPPB) and by hand bulb nebulizers, significant improvement (15% or greater increase in FEV_1) occurred within 5 to 30 minutes and persisted for periods varying from 2 to 6 hours.

In these studies, the longer duration of effect occurred in the studies in which the drug was administered by IPPB, i.e. 6 hours versus 2 to 3 hours when administered by hand bulb nebulizer. In these studies the doses used were 0.3 mL by IPPB and 10 inhalations by hand bulb nebulizer.

In controlled repetitive dosing studies by IPPB and by hand bulb nebulizer the onset of effect occurred within 5 to 30 minutes and duration ranged from 4 to 6 hours. In these studies the doses used were 0.3 mL b.i.d. or t.i.d. when given by IPPB and 10 inhalations q.i.d. (no more often than q 4h) when given by hand bulb nebulizer. As in the single dose studies, effectiveness was measured as a sustained increase in FEV_1 of 15% or greater. In these repetitive dosing studies there was no apparent difference in duration between the two methods of delivery.

During other clinical tolerance studies, metaproterenol was administered q.i.d. (by nebulizer) for periods of 60 and 90 days. On specified days before, during and after these open label trials, patients were referred to a laboratory where the effects of single doses of metaproterenol and isoproterenol on pulmonary function were recorded (in a double blind crossover controlled setting). Both drugs continued to exert significant improvement in function throughout this period of treatment.

CONTRAINDICATIONS

Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore, Metaproterenol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of metaproterenol sulfate as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of sympathomimetic amine aerosol.

PRECAUTIONS

General
Because Metaproterenol Sulfate Inhalation Solution is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

Information for Patients
Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent such as epinephrine or isoproterenol.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed. Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C
Metaproterenol sulfate has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose; the teratogenic effects included skeletal abnormalities and hydrocephalus with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose. There are no adequate and well-controlled studies in pregnant women. Metaproterenol Sulfate Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Metaproterenol Sulfate Inhalation Solution is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS
Adverse reactions are similar to those noted with other sympathomimetic agents.
The most frequent adverse reactions to metaproterenol sulfate are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients, and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

OVERDOSAGE
The symptoms of overdosage are those of excessive beta-adrenergic stimulation listed under ADVERSE REACTIONS. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

DOSAGE AND ADMINISTRATION
Metaproterenol Sulfate Inhalation Solution is for administration with the aid of an intermittent positive pressure breathing apparatus (IPPB) or air driven nebulizer. The usual adult dose is one vial per nebulization treatment. Each vial of 0.4% is equivalent to 0.2 mL Metaproterenol Sulfate Inhalation Solution 5% diluted 2.5 mL with Normal Saline. Each vial of 0.6% is equivalent to 0.3 mL Metaproterenol Sulfate Inhalation Solution 5% diluted to 2.5 mL with Normal Saline.
Usually, treatment need not be repeated more often than every four hours to relieve acute attacks of bronchospasm. As part of a total treatment program in chronic bronchospastic pulmonary diseases, Metaproterenol Sulfate Inhalation Solution may be administered three or four times a day.
As with all medications, the physician should begin therapy with the lowest effective dose and then titrate the dosage according to the individual patient’s requirements.
Meteproterenol Sulfate Inhalation Solution is not recommended for use in children under 12 years of age.

HOW SUPPLIED
Unit-dose plastic vial for inhalation. Cards of five vials are placed into a foil pouch. 25 vials per carton.
NDC 49502-676-24

0.6% Metaproterenol Sulfate Inhalation Solution, 2.5 mL vials. Equivalent to 0.3 mL Metaproterenol Sulfate Inhalation Solution 5% diluted to 2.5 mL Normal Saline. Total contents 15 mg of Metaproterenol Sulfate.
NDC 49502-678-24
0.4% Metaproterenol Sulfate Inhalation Solution, 2.5 mL vials. Equivalent to 0.2 mL Metaproterenol Sulfate Inhalation Solution 5% diluted to 2.5 mL with Normal Saline. Total contents 10 mg of Metaproterenol Sulfate.

Storage
Protect from light. Store in pouch until time of use. Do not store above 25°C (77°F). Do not use if solution is pinkish or darker then slightly yellow in color or contains a precipitate.

Rx only.

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